

ORIGINAL ARTICLE

Natalizumab Induction and Maintenance Therapy for Crohn's Disease

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ABSTRACT

BACKGROUND

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N Engl J Med 2005;353:1912-25.
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Natalizumab, a humanized monoclonal antibody against α_4 integrin, inhibits leukocyte adhesion and migration into inflamed tissue.

METHODS

We conducted two controlled trials to evaluate natalizumab as induction and maintenance therapy in patients with active Crohn's disease. In the first trial, 905 patients were randomly assigned to receive 300 mg of natalizumab or placebo at weeks 0, 4, and 8. The primary outcome was response, defined by a decrease in the Crohn's Disease Activity Index (CDAI) score of at least 70 points, at week 10. In the second trial, 339 patients who had a response to natalizumab in the first trial were randomly reassigned to receive 300 mg of natalizumab or placebo every four weeks through week 56. The primary outcome was a sustained response through week 36. A secondary outcome in both trials was disease remission (a CDAI score of less than 150).

RESULTS

In the first trial, the natalizumab and placebo groups had similar rates of response (56 percent and 49 percent, respectively; $P=0.05$) and remission (37 percent and 30 percent, respectively; $P=0.12$) at 10 weeks. Continuing natalizumab in the second trial resulted in higher rates of sustained response (61 percent vs. 28 percent, $P<0.001$) and remission (44 percent vs. 26 percent, $P=0.003$) through week 36 than did switching to placebo. Serious adverse events occurred in 7 percent of each group in the first trial and in 10 percent of the placebo group and 8 percent of the natalizumab group in the second trial. In an open-label extension study, a patient treated with natalizumab died from progressive multifocal leukoencephalopathy, associated with the JC virus, a human polyomavirus.

CONCLUSIONS

Induction therapy with natalizumab for Crohn's disease resulted in small, nonsignificant improvements in response and remission rates. Patients who had a response had significantly increased rates of sustained response and remission if natalizumab was continued every four weeks. The benefit of natalizumab will need to be weighed against the risk of serious adverse events, including progressive multifocal leukoencephalopathy. (ClinicalTrials.gov numbers, NCT00032786 and NCT00032799.)

THE PATHOGENESIS OF CROHN'S DISEASE involves persistent recruitment of leukocytes into gut tissue, with resultant inflammation. Natalizumab (Tysabri, Elan Pharmaceuticals and Biogen Idec), a humanized IgG4 monoclonal antibody that blocks the adhesion and subsequent migration of leukocytes into the gut by binding α_4 integrin, is a member of a new class of molecules referred to as selective adhesion-molecule inhibitors.¹ Previous studies have suggested that natalizumab may be effective for the treatment of active Crohn's disease.^{2,3} Furthermore, natalizumab has been shown to be effective in the treatment of multiple sclerosis, another chronic inflammatory disease.^{4,5} Therefore, we conducted a 12-week induction trial of natalizumab in patients with moderate-to-severe Crohn's disease. Patients who had a response to natalizumab were eligible to enroll in a 48-week maintenance trial.

METHODS

Members of the steering committees of the Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) induction trial and the Evaluation of Natalizumab as Continuous Therapy (ENACT-2) maintenance trial and the sponsors designed the studies. The authors had access to all data, participated in the analysis and interpretation of the data, and were members of the publication committee. The academic authors vouch for the completeness and veracity of the data and data analyses.

PATIENTS

The ENACT-1 and ENACT-2 trials were randomized, double-blind, placebo-controlled studies conducted at 142 centers between December 2001 and March 2004. The protocols were approved by the institutional review board at each center. All patients gave written informed consent.

The ENACT-1 trial included patients 18 years of age or older who for at least six months had had Crohn's disease that was moderately to severely active as defined by a baseline Crohn's Disease Activity Index (CDAI)⁵ score of 220 to 450 points (scores range from 0 to 600, with higher scores indicating more severe disease activity). Radiologic or endoscopic evidence was required within 36 months before enrollment and after surgical resection to confirm the presence of active disease. Concurrent therapies, including stable doses of 5-aminosalicylates, prednisolone (25 mg per day or less) or

equivalent, budesonide (6 mg per day or less), azathioprine, mercaptopurine, methotrexate, and antibiotics, were permitted. Patients with the short-bowel syndrome, a stricture with obstructive symptoms, a draining fistula, or an abdominal abscess; those who had undergone ostomy; and those who had received therapy against tumor necrosis factor α (TNF- α) within the preceding three months were excluded. Patients who had a response, as defined below, in the ENACT-1 trial were eligible for the ENACT-2 trial.

STUDY DESIGN

Patients who were eligible for the ENACT-1 trial were randomly assigned in a 4:1 ratio to receive an intravenous infusion of either 300 mg of natalizumab or placebo at weeks 0, 4, and 8 and were then followed through week 12. Treatment allocation was prospectively stratified according to disease activity (a CDAI score of less than 330 points vs. a score of at least 330 points) and the use of corticosteroids. The primary efficacy end point of the ENACT-1 trial was the proportion of patients with a response at the prespecified time of week 10. A response was defined as a reduction in the CDAI score of at least 70 points from week 0, whereas remission was defined as a CDAI score of less than 150 points.⁶

Patients with a CDAI score of 0 to 220 at week 12 who had had a response at both weeks 10 and 12 without the need for intervention were eligible for the ENACT-2 trial. Eligible patients were randomly reassigned in a 1:1 ratio to receive an infusion of either placebo or 300 mg of natalizumab every four weeks from weeks 12 through 56 and were followed until week 60. Treatment allocation was prospectively stratified according to disease activity (remission vs. mildly active disease) and the use of corticosteroid therapy and immunosuppressive therapy. The primary efficacy end point of the ENACT-2 study was the proportion of patients treated with natalizumab who had a clinical response in the ENACT-1 study, who were randomly reassigned in the ENACT-2 trial, and who had a sustained response through the prespecified time of week 36. Loss of response was defined by an increase in the CDAI score of at least 70 points after week 12 and by an absolute score of at least 220 or the need for intervention after week 12. Loss of remission was defined as an increase in the CDAI score to at least 150 points or the need for intervention among patients in remission at week 12. Pa-

tients receiving placebo in the ENACT-1 study who were enrolled in the ENACT-2 study were also assessed in exploratory analyses.

Both trials were centrally randomized. Patients and investigators were unaware of treatment assignments.

The doses of all concurrent medications, except corticosteroids, remained constant. Patients receiving concomitant corticosteroids were required to attempt discontinuation according to a fixed tapering regimen. After week 10, the daily dose of prednisolone or equivalent was reduced by 5 mg weekly until a dose of 10 mg was reached. Thereafter, the dose was reduced by 2.5 mg each week until the drug was discontinued. After week 10, the daily dose of budesonide was decreased by 3 mg every three weeks until the drug was discontinued.

EFFICACY AND SAFETY EVALUATIONS

Patients were assessed two weeks before randomized treatment was begun, on day 0, and every two weeks thereafter through week 12 in the ENACT-1 trial. In the ENACT-2 study, patients were assessed every four weeks through week 60. The CDAI score was determined at each visit, adverse events and concomitant medications were recorded, and samples were collected for laboratory evaluations. Safety evaluations included assessment of vital signs, physical examination, hematologic analysis, serum biochemical analysis, and urinalysis.

STATISTICAL ANALYSIS

We estimated that a minimum of 845 patients would be needed for the ENACT-1 study to have a statistical power of 90 percent to detect an absolute difference in response rates of 15 percent between the natalizumab and placebo groups, assuming a 55 percent rate of response to natalizumab, a 40 percent rate of response to placebo, and a 10 percent rate of responses that could not be evaluated. We anticipated that 380 patients who were treated with natalizumab in the ENACT-1 study would have a response, of whom at least 285 would elect to enroll in the ENACT-2 study. We estimated that 285 patients would need to undergo rerandomization for the ENACT-2 study to have a statistical power of 90 percent to detect an absolute difference of 21 percent in the rates of a sustained response, given a 65 percent rate of sustained response to natalizumab, a 44 percent rate for placebo, and a 10 percent rate of responses that could not be evaluated.

Logistic regression was used to analyze differ-

ences in the primary outcome measures, after adjustment for disease activity and corticosteroid use at week 0 in the ENACT-1 study and for the use of corticosteroids and immunosuppressants at week 0 as well as the rates of remission at week 12 in the ENACT-2 trial. Fisher's exact tests were used for analyses of adverse events. The primary analyses had an α level of 0.05 and used two-sided tests. Data from the ENACT-1 trial were analyzed according to the intention-to-treat principle. Efficacy analyses in the ENACT-2 trial excluded patients who underwent randomization despite the lack of a clinical response or remission in the ENACT-1 study. For continuous outcomes, efficacy data collected after intervention or early discontinuation were replaced by the last available value. For the calculation of induction and maintenance of clinical response or remission and corticosteroid-withdrawal end points, patients who required rescue therapy or those with missing data were classified as having no response to treatment.

Logistic regression and log-rank tests were used as appropriate to provide nominal P values for secondary end points. The time to clinical response and time to remission were evaluated by the Kaplan–Meier method and a Cox proportional-hazards model. For the ENACT-1 study, post hoc analyses were also performed to explore the effect of natalizumab in subpopulations with objectively determined active inflammation and chronic disease despite the use of conventional therapies (patients with an elevated concentration of C-reactive protein, those receiving immunosuppressants, and those who had previously received therapy against TNF- α). No adjustments were made for multiple comparisons.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Figure 1 summarizes the disposition of patients. In both trials, the baseline characteristics of the patients were generally similar in the two groups (Table 1). In the ENACT-2 trial, there were significant but clinically unimportant differences between groups in the percentages of men enrolled, CDAI scores, and smoking status.

EFFICACY IN THE ENACT-1 TRIAL

At week 10, 49 percent of patients in the placebo group had had a response (88 of 181), as compared with 56 percent of patients in the natalizumab group

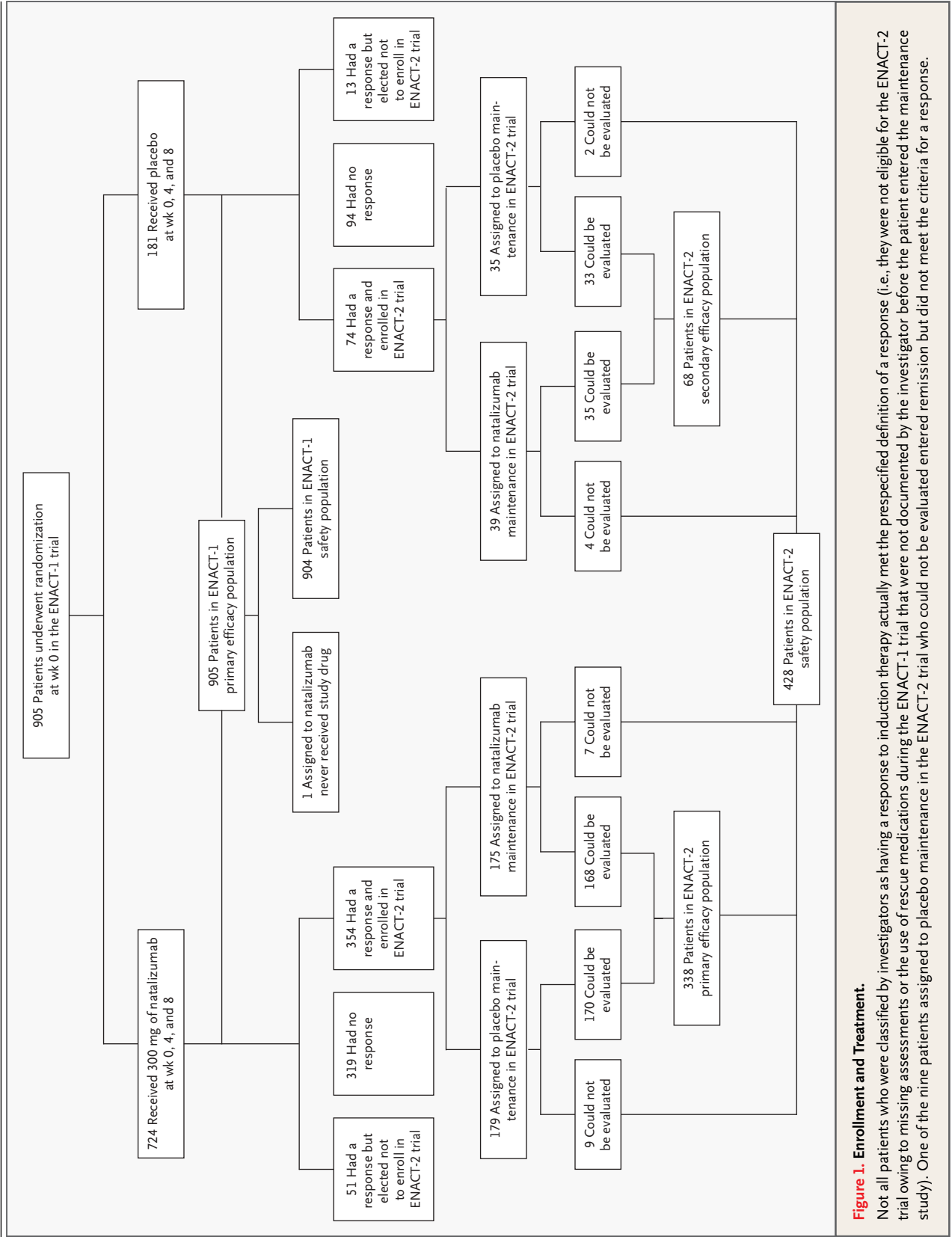


Figure 1. Enrollment and Treatment.

Not all patients who were classified by investigators as having a response to induction therapy actually met the prespecified definition of a response (i.e., they were not eligible for the ENACT-2 trial owing to missing assessments or the use of rescue medications during the ENACT-1 trial that were not documented by the investigator before the patient entered the maintenance study). One of the nine patients assigned to placebo maintenance in the ENACT-2 trial who could not be evaluated entered remission but did not meet the criteria for a response.

Table 1. Baseline Characteristics of the Patients in the ENACT-1 Trial and the Patients Who Had a Response to Natalizumab or Remission at the Time of Randomization in the ENACT-2 Trial.*

Characteristic	ENACT-1 Trial			ENACT-2 Trial
	Placebo (N=181)	Natalizumab (N=724) [†]	Rerandomization to Placebo (N=171) [†]	Rerandomization to Natalizumab (N=168)
Male sex — no. (%)	73 (40)	311 (43)	59 (35)	77 (46) [‡]
Age — yr	39±14	38±12	37±12	37±13
Weight — kg	71±18	72±18	73±17	74±18
Duration of disease — mo	110±93	121±92	116±88	119±95
Intestinal area involved — no. (%)				
Ileum	47 (26)	194 (27)	40 (23)	41 (24)
Ileum and colon	84 (46)	373 (52)	85 (50)	85 (51)
Colon	49 (27)	157 (22)	46 (27)	42 (25)
Data missing or no drug given	1 (1)	0	0	0
Previous segmental resection — no. (%)	73 (40)	300 (41)	69 (40)	55 (33)
CDAI score [§]	303±65	302±60	118±57	105±54 [‡]
C-reactive protein				
Elevated at wk 0 — no. (%) [¶]	134 (74)	526 (73)	129 (75)	129 (77)
Week 0 — mg/liter				
Mean	23±26	20±31	22±32	20±27
Median	12	9	11.3	8.3
Range	0–127	0–370	0–236	0–145
Week 12 — mg/liter [¶]				
Mean	—	—	9.4±16.7	8.9±13.9
Median	—	—	3.9	4.3
Range	—	—	0–120	0–97
Elevated at wk 12 — no. (%) [¶]	—	—	100 (58)	102 (61)
Concomitant medication — no. (%)				
Corticosteroids	70 (39)	271 (37)	76 (44)	64 (38)
Prednisone	53 (29)	197 (27)	54 (32)	44 (26)
Budesonide	20 (11)	79 (11)	24 (14)	21 (13)
Immunosuppressants	52 (29)	247 (34)	60 (35)	62 (37)
Azathioprine	38 (21)	167 (23)	45 (26)	42 (25)
Mercaptopurine	8 (4)	49 (7)	7 (4)	12 (7)
Methotrexate	6 (3)	31 (4)	8 (5)	8 (5)
Antibiotics**	12 (7)	43 (6)	10 (6)	15 (9)
5-Aminosalicylates ^{††}	80 (44)	343 (47)	93 (54)	76 (45)
≥1 Corticosteroids or immunosuppressants	100 (55)	407 (56)	103 (60)	96 (57)
Corticosteroids and immunosuppressants	22 (12)	111 (15)	33 (19)	30 (18)
Previous receipt of therapy against TNF-α — no. (%)	69 (38)	291 (40)	68 (40)	55 (33)
Refractory to such therapy — no. (%)	46 (25)	196 (27)	40 (23)	32 (58)
Current smoker (>10 cigarettes/day) — no. (%)	44 (24)	164 (23)	45 (26)	27 (16) [‡]

* Plus–minus values are means ±SD.

[†] The total includes one patient who entered remission and did not meet the criteria for response.

[‡] P<0.05 for the comparison with patients with a response to natalizumab who were randomly reassigned to placebo.

[§] Scores for the Crohn's Disease Activity Index (CDAI) can range from 0 to 600; higher scores indicate more severe disease activity.

[¶] The normal range is 2.87 mg per liter or less.

^{||} P<0.05 for the comparison with patients who were randomly assigned to placebo.

** This category included metronidazole, tinidazole, ciprofloxacin, and clarithromycin.

^{††} This category included mesalamine, sulfasalazine, and olsalazine.

(408 of 724, $P=0.05$) (Fig. 2A). Similarly, 30 percent of patients in the placebo group were in remission at week 10 (55 of 181), as compared with 37 percent of patients in the natalizumab group (267 of 724, $P=0.12$) (Fig. 2B). The differences between the natalizumab and placebo groups were significant at week 10 with the use of the more stringent definition of response as a 100-point decrease in the CDAI score. The rates of response and remission were higher in the natalizumab group at all times, but the majority of these differences were not significant (Fig. 2A and 2B). The results among patients receiving corticosteroids at baseline were similar to those overall.

In contrast, the efficacy of natalizumab was demonstrated in the subgroups of 660 patients with an elevated concentration of C-reactive protein at baseline (upper limit of normal, 2.87 mg per liter), 300 patients with active disease despite the use of immunosuppressants, and 358 patients who had previously received anti-TNF- α therapy. Each subgroup was significantly more likely to have either a response or a remission after treatment with natalizumab than after receiving placebo (Fig. 2C and 2D). The rates of response and remission were also higher, but not significantly so, among natalizumab-treated patients in the subgroup who had not previously received anti-TNF- α therapy and the subgroup with active disease and no concomitant use of immunosuppressants but not in the subgroup without an elevated concentration of C-reactive protein at baseline (Fig. 2C and 2D). The dose of natalizumab (in milligrams per kilogram of body weight) had no significant effect on the rates of response or remission.

THE ENACT-2 TRIAL

Efficacy among Patients with a Response to Natalizumab in the ENACT-1 Trial

In the ENACT-2 trial, 28 percent of patients randomly reassigned to placebo had a sustained response through week 36 (48 of 170), as compared with 61 percent of patients randomly reassigned to natalizumab (103 of 168, $P<0.001$) (Fig. 3A). Regression analyses demonstrated that adjustment for sex, baseline CDAI scores, smoking status, C-reactive protein concentration (at week 0 or 12), the use of prior anti-TNF- α therapy, and the dose of natalizumab did not influence the results. Overall, 26 percent of patients in the placebo group had a sustained remission through week 36 (31 of 120), as compared with 44 percent of patients in the natali-

zumab group (57 of 130, $P=0.003$) (Fig. 3B). The rates of sustained response and remission were significantly higher in the natalizumab group at every point beginning at week 20 and continuing through week 60 (Fig. 3A and 3B). The natalizumab group also had significantly higher rates of response and remission rates when the results were assessed at prespecified points (weeks 36 and 60) (Fig. 3C).

The median time to the loss of response was 86 days in the placebo group and more than 336 days in the natalizumab group ($P<0.001$). Among patients who entered remission after induction therapy with natalizumab, the median time to the loss of remission was 59 days in the placebo group and 137 days in the natalizumab group ($P<0.001$).

Forty-two percent of patients who had a response to induction therapy with natalizumab (143 of 339) had received oral corticosteroids or budesonide at baseline. Among patients who completed week 36 of the ENACT-2 study, 28 percent of those randomly reassigned to placebo were no longer taking corticosteroids, as compared with 58 percent of patients randomly reassigned to natalizumab ($P<0.001$); the results were similar at week 60 ($P<0.001$). At week 36, 22 percent of patients in the placebo group who received corticosteroid therapy at baseline were in remission and had discontinued corticosteroids, as compared with 45 percent of patients in the natalizumab group ($P=0.01$); the results were similar at week 60 ($P=0.001$) (Fig. 3D).

Efficacy among Patients with a Response to Placebo in the ENACT-1 Trial

Among the patients who had a response to induction therapy with placebo at the time of randomization, 55 percent of patients who were randomly reassigned to placebo maintained a response through week 36 (18 of 33), as compared with 54 percent of patients who were randomly reassigned to natalizumab (19 of 35, $P=0.58$). Similarly, 36 percent of patients who were randomly reassigned to placebo maintained a response through week 60 (12 of 33), as compared with 49 percent of patients who were randomly reassigned to natalizumab (17 of 35, $P=0.16$).

SAFETY

Table 2 shows the overall incidence of adverse events. Two patients treated with natalizumab died during or after participation in the ENACT-1 study. The first patient died of asphyxiation resulting from an occupational accident, as determined by a sub-

sequent government investigation. The second patient died from complications of surgery for a severe exacerbation of Crohn's disease 28 weeks after completing the study. No deaths occurred during the ENACT-2 study. No hematologic cancers occurred during either study. Basal-cell carcinoma of the skin developed in one patient in each group during the ENACT-2 study. There were no clinically significant changes in laboratory values in either treatment group in either trial. Natalizumab-treated patients had moderate and sustained elevations in the median absolute circulating lymphocyte count (not above the upper limit of normal; 2900 and 2800 cells per cubic millimeter at weeks 10 and 36, respectively), as compared with baseline (1600 cells per cubic millimeter), a predicted pharmacologic effect, reversible on cessation of treatment with natalizumab.

Table 2 shows the overall incidence of infections. Influenza and influenza-like illness occurred more frequently in the natalizumab group than in the placebo group in the ENACT-2 trial. Specific types of serious infections observed in each group are shown in Table 2. During the ENACT-2 trial, there was one report each of varicella pneumonia (after exposure to a child who had varicella-zoster) and cytomegalovirus hepatitis judged by the investigator not to be serious, both in natalizumab-treated patients. Both resolved with appropriate medical therapy, and there were no sequelae. In addition, one patient who received three doses of natalizumab in combination with azathioprine during the ENACT-1 study, nine doses of placebo in combination with azathioprine during the ENACT-2 study, and five doses of natalizumab without azathioprine during an open-label extension study after early discontinuation from the ENACT-2 study died from progressive multifocal leukoencephalopathy associated with the JC virus, a human polyomavirus.

During the ENACT-1 study, acute infusion reactions (any adverse event occurring within 120 minutes after the initiation of an infusion) occurred in 8 percent of patients in the placebo group and 11 percent of those who received natalizumab; the corresponding rates for the ENACT-2 study were 8 percent and 7 percent (Table 2). Hypersensitivity-like reactions occurred in 2 percent of patients in the placebo group and 5 percent of those in the natalizumab group in the ENACT-1 study; the corresponding rates in the ENACT-2 study were 1 percent and 3 percent (Table 2).

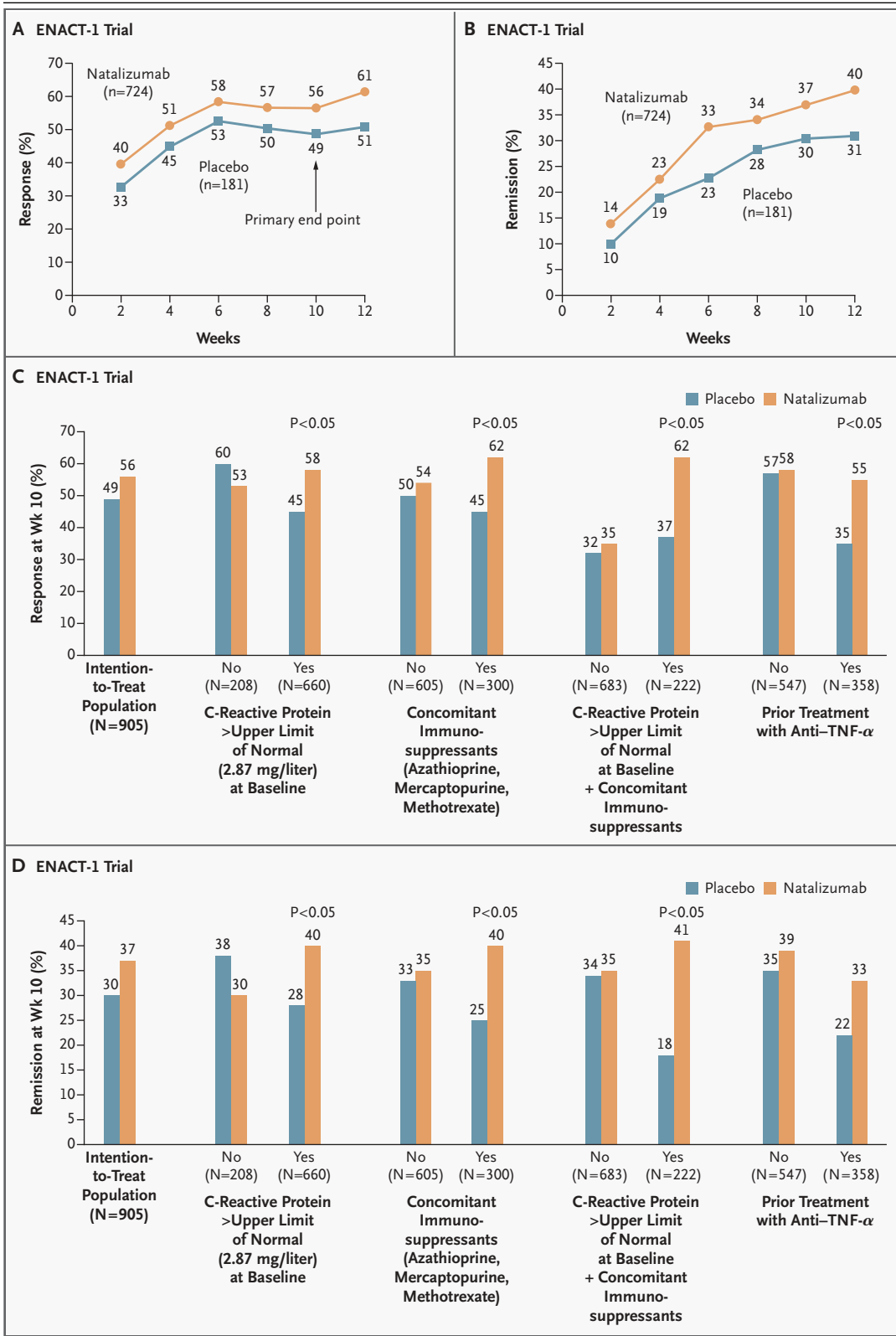
Figure 2 (facing page). Percentage of Patients in the ENACT-1 Trial with a Clinical Response at Each Visit (Panel A), in Remission at Each Visit (Panel B), with a Response at Week 10 (Panel C), and in Remission at Week 10 (Panel D).

A response was defined as a decrease from baseline in the CDAI score of at least 70 points. Remission was defined as a decrease in the CDAI score to less than 150 points. Significant differences between the treatment groups are shown.

IMMUNOGENICITY

Of the patients exposed to natalizumab during either study, 8 percent in the ENACT-1 study (53 of 650) and 9 percent in the ENACT-2 study (36 of 390) tested positive for antibodies against natalizumab (a positive test was defined as a concentration of at least 0.5 μg per milliliter at any time on at least one occasion). During the ENACT-2 study, patients were further classified as having persistent antibodies against natalizumab (defined as two positive antibody tests occurring at least six weeks apart or a single positive test at the last measurement) or transient antibodies (defined as antibody-positive but not meeting the definition of persistent antibodies). Patients in the ENACT-1 study could not be further classified because testing for antibodies was not performed until week 12. Six percent of patients in the ENACT-2 study were persistently positive for antibodies against natalizumab (23 of 390), and 3 percent were transiently positive (13 of 390). Testing was performed every 12 weeks during the ENACT-2 study. Concomitant immunosuppressive and corticosteroid therapy appeared to be moderately protective against the formation of antibodies against natalizumab in both trials, but the low overall rates of immunogenicity precluded statistical comparisons (Table 2).

Acute infusion reactions occurred in 45 percent of patients who tested positive for antibodies against natalizumab in the ENACT-1 trial (24 of 53), as compared with 9 percent of patients who tested negative for antibodies (54 of 597, $P < 0.001$). Of 650 patients in the ENACT-1 study who were tested, 5 had a serious hypersensitivity-like reaction, 3 of whom were positive for antibodies against natalizumab. In the ENACT-2 safety population, 19 percent of patients who tested positive for antibodies against natalizumab (7 of 36, all of whom had persistent antibodies) had either an acute infusion reaction (3 patients) or a hypersensitivity-



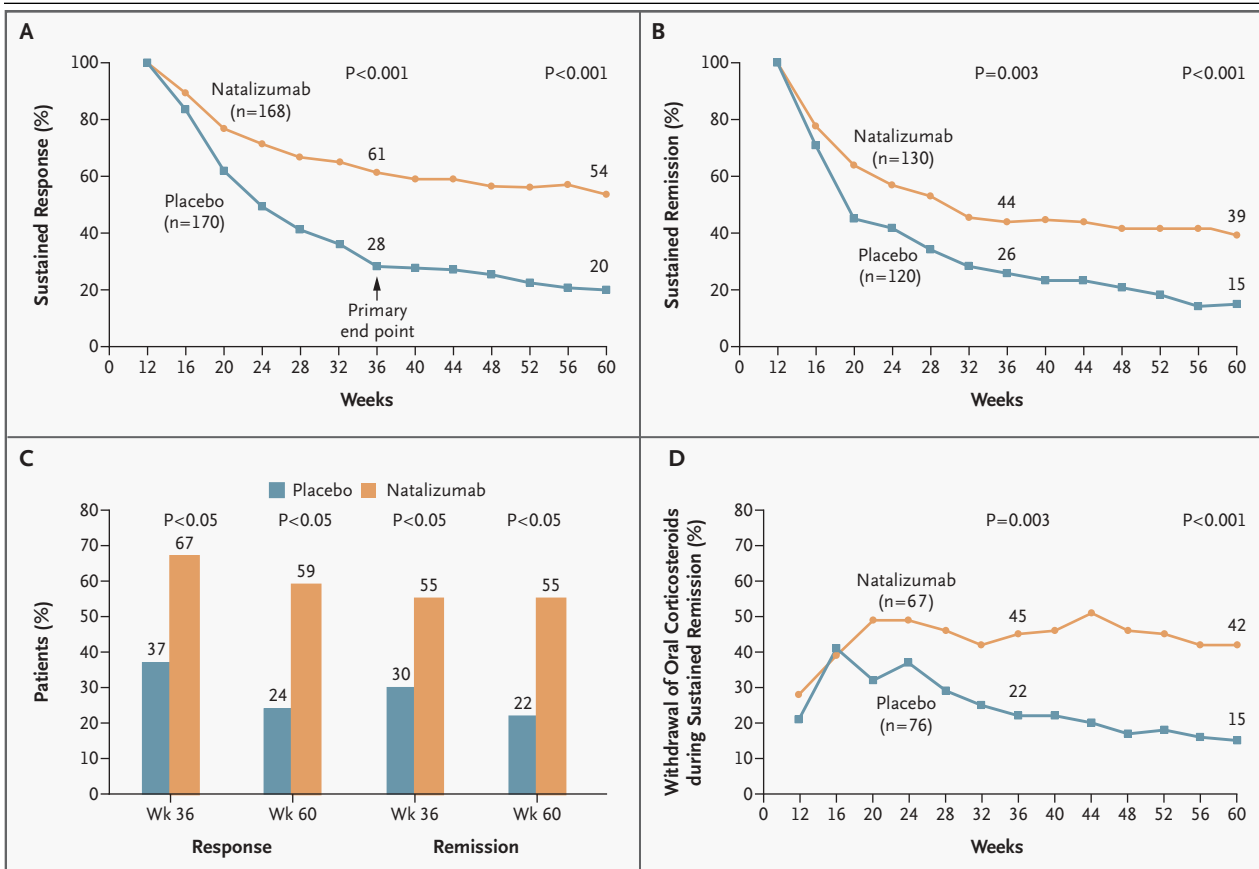


Figure 3. Percentage of Patients in the ENACT-2 Trial with a Sustained Response (Panel A) and Sustained Remission (Panel B) at Each Visit, Percentage of Patients with a Response or Remission at Weeks 36 and 60 (Panel C), and Percentage of Patients Taking Oral Corticosteroids at Randomization in the ENACT-1 Trial Who Were No Longer Taking Oral Corticosteroids While Remaining in Remission during the ENACT-2 Trial (Panel D).

In Panel A, the analysis was limited to patients with a response to natalizumab in the ENACT-1 trial who met the eligibility criteria for the ENACT-2 trial at randomization. In Panel B, the analysis was limited to patients with a response to natalizumab in the ENACT-1 trial who met the eligibility criteria for remission at the time of randomization for the ENACT-2 trial. Loss of response was defined as an increase in the CDAI score after week 12 of at least 70 points to an absolute score of at least 220 or the use of rescue intervention. Loss of remission was defined as an increase in the CDAI score to at least 150 points or the need for intervention in patients in remission at week 12. Significant differences between the treatment groups are shown.

like reaction (4 patients), as compared with 7 percent of patients who tested negative for antibodies (26 of 354, $P=0.02$). Of 390 patients (2 percent) in the ENACT-2 study who were tested, 8 had a hypersensitivity-like reaction, 4 of whom were persistently positive for antibodies against natalizumab. Although the incidence of acute infusion and hypersensitivity-like reactions was low, these events occurred more frequently among patients with persistent, but not transient, antibodies against natalizumab.

In the ENACT-1 study, of the 8 percent of patients who were treated with natalizumab and who

were positive for antibodies against natalizumab, 53 percent (28 of 53) had a response at week 12, as compared with 62 percent of patients who tested negative for antibodies (371 of 597, $P=0.18$). In the ENACT-2 study, 7 percent of patients who had a response to induction therapy with natalizumab and who were randomly reassigned to natalizumab (11 of 168) tested positive for antibodies against natalizumab (7 of these 11 patients had persistent antibodies). None of these patients with persistent antibodies maintained a response through week 60, as compared with 3 of 4 patients with transient antibodies (75 percent) and 87 of 156 patients who

tested negative for antibodies (56 percent). In addition, median lymphocyte counts over time in the seven patients with persistent antibodies were similar to those in patients receiving placebo, whereas patients with transient antibodies continued to have the expected elevations in circulating lymphocyte counts.

DISCUSSION

In patients with Crohn's disease, induction and sustained maintenance of response and remission (particularly in patients who have had no response to currently available agents), corticosteroid-sparing therapies, and improved drug safety constitute important unmet medical needs. Inhibition of leukocyte adhesion and migration to sites of inflamed tissue represents a unique mechanism of action for the treatment of Crohn's disease. Although the results of the ENACT-1 trial failed to demonstrate that induction treatment with natalizumab was superior to placebo in patients with moderate-to-severe Crohn's disease, the ENACT-2 trial showed that among the group of patients who had a response to natalizumab, response and remission were more likely to be sustained through 60 weeks if natalizumab treatment was continued rather than stopped after three treatments.

Data from two previous phase 2 induction trials suggested that natalizumab may be effective for the induction of a response and remission in patients with moderate-to-severe Crohn's disease. The first double-blind, placebo-controlled study examined the efficacy of a single dose of natalizumab (3 mg per kilogram of body weight) or placebo. The CDAI score decreased by a mean of 45 points among the 18 natalizumab-treated patients, although this reduction was not significantly different from the mean reduction among the 12 patients receiving placebo (11 points).² The second double-blind, placebo-controlled, dose-finding study examined the efficacy of two doses of natalizumab (3 mg or 6 mg per kilogram) in 66 and 51 patients, one dose of natalizumab (3 mg per kilogram, followed by placebo) in 68 patients, or two doses of placebo in 63 patients. The findings of the prespecified primary analysis of remission at week 6 were not significant, but significant differences between natalizumab and placebo were observed at multiple times.³

The ENACT-1 trial failed to demonstrate a significant benefit of natalizumab for induction ther-

apy. A similar phenomenon has been reported in other placebo-controlled trials of a variety of other biologic agents in patients with Crohn's disease.⁷⁻⁹ Subgroup analyses of these other studies have demonstrated that a lower concentration of C-reactive protein was associated with a higher likelihood of a response to placebo. Furthermore, a meta-analysis of factors contributing to higher rates of a response to placebo in induction trials involving patients with active Crohn's disease demonstrated that the duration of the study (greater than eight weeks), the frequency of study visits (less than four weeks apart), and the CDAI score at entry (less than 200 points) were important predictors of the rate of remission in the placebo group, with the duration of the study as the most important independent predictor.¹⁰

To better evaluate the efficacy of natalizumab as an induction agent, we analyzed subpopulations of patients from the ENACT-1 trial who had objectively confirmed active inflammation or chronically active disease despite conventional therapies. These analyses demonstrated significantly greater response and remission rates for natalizumab than for placebo in patients with elevated C-reactive protein concentrations, active disease despite the use of immunosuppressants, or prior receipt of anti-TNF- α therapy. The analyses of patients who did not have these markers of active inflammation showed numerically greater (but not significant) rates of response and remission for natalizumab than for placebo in all the subgroups except patients without an elevated concentration of C-reactive protein at baseline (these patients had numerically greater [but not significant] response and remission rates for placebo than for natalizumab).

In the ENACT-2 maintenance trial, patients who received natalizumab were more than twice as likely as those who received placebo to have a sustained clinical response and almost twice as likely to have a sustained remission. Furthermore, natalizumab treatment had significant corticosteroid-sparing effects; nearly half the natalizumab-treated patients who were receiving corticosteroids at baseline in the ENACT-1 trial were not taking corticosteroids by week 60 of the ENACT-2 study, and more than 40 percent were in remission and corticosteroid-free. An unexpectedly high percentage of patients with a response to placebo in the ENACT-1 trial maintained that clinical benefit in the ENACT-2 trial, whether randomly reassigned to natalizumab or placebo, suggesting that some of these patients may

Table 2. Summary of Safety and Immunogenicity Analyses of All Randomized Patients to Week 12 in the ENACT-1 Trial and to Week 60 in the ENACT-2 Trial.

Adverse Event	ENACT-1 Trial		ENACT-2 Trial	
	Placebo (N=181)	Natalizumab (N=723)	Rerandomization to Placebo (N=214)	Rerandomization to Natalizumab (N=214)
Any adverse event — no. of patients (%)	153 (85)	626 (87)	207 (97)	194 (91)*
Adverse events occurring in ≥10% of either group — no. of patients (%)				
Headache	41 (23)	214 (30)	60 (28)	77 (36)
Nausea	30 (17)	123 (17)	49 (23)	48 (22)
Nasopharyngitis	26 (14)	100 (14)	52 (24)	49 (23)
Abdominal pain	23 (13)	76 (11)	47 (22)	44 (21)
Fatigue	14 (8)	69 (10)	29 (14)	26 (12)
Vomiting	19 (10)	61 (8)	29 (14)	29 (14)
Crohn's disease	19 (10)	45 (6)	84 (39)	30 (14)*
Arthralgia			45 (21)	42 (20)
Back pain			19 (9)	26 (12)
Influenza			11 (5)	25 (12)*
Influenza-like illness			13 (6)	23 (11)
Pharyngitis			22 (10)	23 (11)
Diarrhea			21 (10)	17 (8)
Adverse events leading to discontinuation of study drug — no. of patients (%)	13 (7)	59 (8)	61 (29)	29 (14)*
Serious adverse events — no. of patients (%)	12 (7)	52 (7)	21 (10)	18 (8)
Infections — no. of patients (%)	78 (43)	352 (49)	119 (56)	132 (62)
Specific types of infections with ≥2% higher incidence in the natalizumab maintenance group than in the placebo maintenance group — no. of patients (%)				
Influenza			11 (5)	25 (12)*
Influenza-like illness			13 (6)	23 (11)
Sinusitis			9 (4)	17 (8)
Viral infection			7 (3)	14 (7)†
Vaginal candidiasis			1 (<1)	6 (3)
Herpes zoster			0	4 (2)
Serious infections — no. of patients (%)‡	4 (2)	12 (2)§	5 (2)	6 (3)
Perianal abscess	1 (1)	3 (<1)	2 (1)	2 (1)
Abdominal infection			0	1 (<1)
Intraperitoneal abscess	1 (1)	0		
Psoas abscess	0	1 (<1)		
Peritonitis	0	1 (<1)		
Appendiceal abscess	0	1 (<1)		
Chronic fungal vaginitis			0	1 (<1)
Urinary tract infection			0	1 (<1)
Varicella pneumonia			0	1 (<1)
Upper respiratory tract infection			2 (1)	0
Bronchopneumonia	0	1 (<1)	1 (<1)	0
Sepsis	2 (1)	0		
Prostatitis	0	1 (<1)		
Viral meningitis	0	2 (<1)		
Gastroenteritis	0	2 (<1)		
Viral gastroenteritis	1 (1)	1 (<1)		

Table 2. (Continued.)

Adverse Event	ENACT-1 Trial		ENACT-2 Trial	
	Placebo (N=181)	Natalizumab (N=723)	Rerandomization to Placebo (N=214)	Rerandomization to Natalizumab (N=214)
Acute infusion reaction (any adverse event occurring ≤2 hr after start of infusion) — no. (%)	14 (8)	83 (11)	18 (8)	14 (7)
Hypersensitivity-like reaction — no. (%)	3 (2)	34 (5)	2 (1)	6 (3)
Hypersensitivity-like reaction during an infusion — no. (%)	2 (1)	32 (4)¶	0	5 (2)
Not serious, did not lead to early discontinuation of study drug	0	13 (2)	0	1 (<1)
Not serious, led to early discontinuation of study drug	2 (1)	14 (2)	0	3 (1)
Serious, did not lead to early discontinuation of study drug	0	2 (<1)	0	0
Serious, led to early discontinuation of study drug	0	3 (<1)	0	1 (<1)¶¶
Hypersensitivity-like reaction after an infusion — no. of patients (%)	1 (1)	2 (<1)	2 (1)**	1 (<1)††
Antibodies against natalizumab in ENACT-1 study — no./total no. (%)	0/163	53/650 (8)		
Natalizumab monotherapy	0/73	39/286 (14)		
Natalizumab + oral corticosteroids	0/43	8/141 (6)		
Natalizumab + immunosuppressants	1/47 (2)	6/223 (3)		
Persistently positive for antibodies against natalizumab in ENACT-2 study — no./total no. (%)			13/179 (7)	10/211 (5)‡‡
Natalizumab monotherapy			8/71 (11)	9/88 (10)§§
Natalizumab + oral corticosteroids			3/44 (7)	1/45 (2)¶¶¶
Natalizumab + immunosuppressants			2/64 (3)	0/78

* P<0.05 for the comparison with patients with a response to natalizumab who were randomly reassigned to placebo.
† Nonserious (in the opinion of the investigator) cytomegalovirus hepatitis developed in one patient.
‡ One patient died from progressive multifocal leukoencephalopathy during an open-label extension study.
§ Both peritonitis and an appendiceal abscess developed in one patient.
¶ P<0.05 for the comparison with patients who were randomly assigned to placebo.
¶¶ One patient had a serious hypersensitivity-like reaction during the infusion that required discontinuation of natalizumab and treatment with an antihistamine agent.
** Fever developed in one patient eight hours after the third placebo infusion; antibodies against natalizumab were not present. Another patient had a hypersensitivity-like reaction (diagnosed as serum sickness) four days after the initial placebo infusion. The patient had normal serum complement concentrations and no antibodies against natalizumab.
†† One patient had a hypersensitivity-like reaction (diagnosed as a mild leukocytoclastic vasculitis and confirmed by skin biopsy) four days after the fifth infusion. Serum complement concentrations were normal, and antibodies against natalizumab were not present.
‡‡ Results include 3 of 37 patients (8 percent) who received placebo induction therapy and natalizumab maintenance therapy and 7 of 174 patients (4 percent) who received natalizumab induction therapy and natalizumab maintenance therapy.
§§ Results include 3 of 16 patients (19 percent) who received placebo induction therapy and natalizumab maintenance therapy and 6 of 72 patients (8 percent) who received natalizumab induction therapy and natalizumab maintenance therapy.
¶¶¶ Results include 0 of 10 patients who received placebo induction therapy and natalizumab maintenance therapy and 1 of 35 patients (3 percent) who received natalizumab induction therapy and natalizumab maintenance therapy.
||| Results include 0 of 11 patients who received placebo induction therapy and natalizumab maintenance therapy and 0 of 67 patients who received natalizumab induction therapy and natalizumab maintenance therapy.

not have had active Crohn's disease during the studies.

The incidence of serious adverse events is an important consideration in assessing the risk-benefit ratio of induction and maintenance therapies. The safety profile observed in both studies was similar to those in previous natalizumab studies.^{2-5,11} All these trials lacked adequate statistical power to detect rare serious adverse events. Recently, progressive multifocal leukoencephalopathy associated with the JC virus developed in two patients with multiple sclerosis treated with natalizumab in combination with interferon beta-1a^{12,13} and in one patient with Crohn's disease (described above)¹⁴; two of these patients died. Further evaluation of this serious adverse event in patients who have been treated with natalizumab for any indication is under way.

The incidences of antibodies against natalizumab after induction therapy and of persistent antibodies against natalizumab during maintenance therapy were low. Concomitant use of immunosuppressive agents and corticosteroids, although not required for efficacy, may further reduce the formation of antibodies against natalizumab. When antibodies are persistently present, they appear to be associated with infusion reactions, hypersensitivity-like reactions, and loss of efficacy.

In conclusion, the response to induction therapy was nonsignificantly higher among patients treated with natalizumab than among patients who received placebo. Although the clinical benefit of therapy with natalizumab will ultimately need to be weighed against the potential risk of rare but serious adverse events, maintenance treatment with natalizumab in patients who had a response to natalizumab resulted in significantly higher rates of sustained response and remission and corticosteroid-sparing effects than withdrawal of treatment.

Supported by a research grant from Elan Pharmaceuticals, San Diego, Calif., and Biogen Idec, Cambridge, Mass., and by a grant (M01RR0058, to Dr. Sandborn) from the National Institutes of Health.

Dr. Sandborn reports having served as a consultant and having received speaker's fees and grant support from Elan. Dr. Colombel reports having served as a consultant for and receiving speaker's fees from Elan. Dr. Feagan reports having received consulting fees from Elan. Dr. Hanauer reports having received consulting fees and research support from Elan. Drs. Panaccione and Sanders report having served as consultants for Elan. Dr. Targan reports having received lecture fees from Elan. Drs. van Deventer and Rutgeert report having received consulting fees and lecture fees from Elan. Drs. Goldblum and Hogge and Mr. Despaigne are employees of Elan and report owning Elan stock options.

We are indebted to Drs. Allison Hulme and Evan Beckman, Ms. Tanya Palmer, and Ms. Cooleen Twohig for their valuable contributions during the conduct of this study; to Dr. Chito Hernandez for statistical advice and analysis; and to Drs. Jeannie Giacchino, Jeffrey Bornstein, Lisa Shackleton, Josefina Cruz-Jain, Mr. Christopher Tennant, and Ms. Michele Libonati for critical review and editorial advice during the preparation of this manuscript.

APPENDIX

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